Remarks and Arguments

Claims 1-12 were presented for examination. Claim 1 has been amended.

Claims 1-3, 7 and 8 have been rejected under 35 U.S.C. §102(b) as anticipated by U.S. Patent Publication No. US 2002/0139751 A1 (Zhang, previously cited.) The examiner is correct in stating that, in the Zhang reference, an entire sample is fractionated into multiple discrete fractions in a series format during a first separation step. This is set forth in Zhang paragraph [0072], which discloses that a single column is loaded with the entire sample and "[t]he effluents containing the separated target molecules under stepwise elution with different concentrations of the counter-ions (salts) are delivered to the reservoir array from low to high concentrations of counter-ions. As a result, the separated molecules in different reservoirs of the microchip are electrosprayed and identified by ESI/MS."

This first separation step in the column corresponds to "a first fractionating dissolution by contacting the mixture to a surface and sequentially dissolving biosubstances through specially adjusted solvents" as recited in Claim 1.

In Zhang, the eluted fractions are collected in spatially separated reservoirs of the microchip array, i.e., there are "multiple discrete fractions" as recited in Claim 1. In addition, each reservoir of the microchip array can contain different adsorbents capable of retaining specific classes of biosubstances in the reservoirs. This is set forth in Zhang paragraph [0071] which states: "Typically, the capillary column contains the adsorbent less specific or suitable for binding of a serial similar analytes, while the chip array contains the adsorbents more specific or suitable for secondary affinity separation of the retained classes of analytes."

However, in Zhang, the biosubstances that are not retained in the reservoirs are electrosprayed from the respective reservoirs and analyzed by mass spectrometry. Consequently, the second separation step does not result in multiple discrete sub-fractions, as recited in claim 1, but in exactly one sub-fraction that is electrosprayed. The Zhang reference is silent whether biosubstances, which are retained in the reservoirs, are further processed and analyzed. Thus, Zhang does not teach that "separated biosubstances in each discrete fraction are further successively separated into a plurality of discrete sub fractions using a second fractionating binding on solid

surfaces or a second fractionating dissolution from a surface through specially adjusted solvents." as recited in lines 8-12 of amended claim 1.

In addition, Figure 9 of the Zhang reference shows "the reservoir-side of the chip with an 8 x 12 array, wherein the 8 columns (in the vertical direction) have 8 different affinity adsorbents while each column (in the horizontal direction) has the same adsorbent." (see Zhang, paragraph [0059]). In this embodiment, each fraction of the first separation step is divided into equal 8 aliquots which are transferred to the 8 columns of one row of the microchip array. Since the fractions are divided, the second separation step can not be regarded as a separation step in a series of separations. In contrast, in the present invention, substantially all of the separated biosubstances in each discrete fraction is used for the second separation step (amended claim 1, lines 8-9); therefore, each sub-fraction contains more molecules of the respective biosubstances compared to the Zhang reference. Therefore, claim 1 patentably distinguishes over the Zhang reference.

Claims 2-3, 7 and 8 are dependent on amended claim 1 and incorporate the limitations thereof. Therefore they also distinguish over the Zhang reference in the same manner as amended claim 1distinguishes over the Zhang reference.

Claims 1-3, 5, 6, 11 and 12 have been rejected under 35 U.S.C. §102(b) as anticipated by U.S. Patent Publication No. US 2002/0068366 A1 (LaDine, previously cited.) The examiner states that LaDine discloses that an entire sample is separated into fractions and sub-fractions (as taught in paragraphs [0095] and [0096]) in a series format. However, the LaDine reference is completely silent at paragraphs [0092] to [0114] whether a sample is fractionated in series or in parallel. In contrast to these cited paragraphs, LaDine teaches in paragraph [0028]:

> "In the embodiment illustrated, the sample holders are the wells of a microplate 15 that is used in a parallel magnetic particle separation apparatus, which will be described in detail below. Briefly, the wells are held in a well tray or microplate 15. Each raw lysate sample from aliquot A and aliquot B is divided into six portions placed into six wells in the first row 7 of the microplate 15. The samples are treated by magnetic particle separation to separate and wash proteins using the wells in rows 8, 9. For example, the separation may be according to subcellular location or gross physicochemical characteristic. In this illustration, samples at each time

interval are provided in six wells so that up to six different separation schemes may be coordinated in parallel."

Consequently, it is believed that LaDine teaches a parallel work flow. The fractionating performed in LaDine is limited by initially splitting up of the entire sample into starting aliquots. Therefore, the number of the respective biosubstances in the resulting fractions and sub-fractions is in principle less than in the present invention. Consequently, amended claim 1 patentably distinguishes over the LaDine reference in the same manner as it distinguishes over the Zhang reference as discussed above.

Claims 2-3, 5, 6 11 and 12 are dependent on amended claim 1 and incorporate the limitations thereof. Therefore they also distinguish over the LaDine reference in the same manner as amended claim 1distinguishes over the LaDine reference.

Claim 4 has been rejected under 35 U.S.C. §103(a) as obvious over the LaDine reference in view of U.S. Patent No. 5,240,602 (Hammen, previously cited.) As noted in a response filed on September 24, 2007, wherein the Hammen reference is discussed in detail, only one separation is disclosed in Hammen. Amended claim 1 clearly recites that at least two sequential separations are performed both with either affinity binding to a solid surface of solvent-based dissolution. These sequential separations are not disclosed in LaDine, which discloses parallel separation as discussed above, or in Hammen. Thus, claim 1 patentably distinguishes over the combination of the LaDine and Hammen references. Claim 4 is dependent on claim 1 and incorporate the limitations thereof. Therefore, it distinguishes over the cited reference combination in the same manner as claim 1.

Claims 9 and 10 have been rejected under 35 U.S.C. §103(a) as obvious over the Zhang reference in view of U.S. Patent No. 5,240,604 (Cortes, previously cited.) The Cortes reference was also discussed in detail in the response filed on September 24th. The combination of Cortes with Zhang does not add to Zhang the sequential multi-dimensional fractionation that is discussed above with respect to Zhang and amended claim 1. Consequently, the combination of Zhang and Cortes does not teach or suggest the invention recited in claim 1. Since claims 9 and 10 are dependent on claim 1 and incorporate the limitations thereof, they distinguish over the cited reference in the same manner as claim 1.

In light of the forgoing amendments and remarks, this application is now believed in condition for allowance and a notice of allowance is earnestly solicited. If the examiner has any further questions regarding this amendment, he is invited to call applicants' attorney at the number listed below. The examiner is hereby authorized to charge any fees or direct any payment under 37 C.F.R. §§1.17, 1.16 to Deposit Account number 50-3969.

Respectfully submitted

/paul e. kudirka/ Date: 2008-09-15

Paul E. Kudirka, Esq. Reg. No. 26,931
LAW OFFICES OF PAUL E. KUDIRKA
Customer Number 64967
Tel: (617) 357-0010 Fax: (617) 357-0035